

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: Whitehouse  
Serial No. 09/901,428  
Filed : July 9, 2001  
Examiner: Kiet Tuan Nguyen  
Art Unit: 2881  
For: Multiple Ion Guide  
Attorney Docket No. 840.052.203

April 6, 2009

**VIA EFS**

Hon. Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

**BRIEF ON APPEAL**

This brief is submitted to the Board of Patent Appeals and Interferences in support of Applicant's appeal from the final rejection of the Examiner having a mailing date of June 17, 2008.

**REAL PARTY IN INTEREST**

Analytica of Branford, Inc.

**RELATED CASES**

An amendment to provoke an interference was filed on September 3, 2002.

A Notice of Appeal was filed on February 10, 2005 and an Appeal Brief was submitted on July 11, 2005. These documents were prepared and filed by Peter L. Berger (24,570). The application was returned to prosecution subsequent to the Appeal Brief of 2005.

A Pre-Brief Conference Request was filed on October 29, 2008, for which a decision was mailed on February 5, 2009.

### JURISDICTIONAL STATEMENT

The Board has jurisdiction under 35 U.S.C. 134(a). The Examiner mailed a final rejection on June 17, 2008, setting a three-month shortened statutory period for response. On October 29, 2008, Applicant petitioned for a two-month extension of time and filed a Notice of Appeal concurrently with a Pre-Appeal Brief Request. Applicant received a Notice of Panel Decision on February 5, 2009 setting a time period for filing an Appeal Brief at one month from February 5, 2008 or the balance of the two-month time period from the filing of a Notice of Appeal. Because the two-month time period for filing an Appeal Brief had expired by the mailing of the Panel Decision, the applicable deadline is one month from said mailing, which is March 5, 2008. The one month time period is extendible under 37 CFR 1.136. Applicant submits herewith a petition for a one-month extension of time to file an Appeal Brief along with the requisite fees. A one-month extension of time set the deadline to respond on Monday April 6, 2009. The appeal brief is being filed on April 6, 2009.

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## TABLE OF AUTHORITIES

None.

## STATUS OF AMENDMENTS

Applicant filed a preliminary amendment concurrently with a request for continued examination on April 18, 2008. Applicant amended the specification to recite that the application is a “continuation in part” (replacing “continuation”). The Examiner did not indicate whether or not he entered this amendment.

## GROUND OF REJECTION TO BE REVIEWED

### OBJECTED DRAWINGS

The Drawings were objected to under 37 CFR 1.83(a) for not showing every feature of the invention specified in the Claims. The Examiner required Drawings that show a “means for providing a delay between the release of the pulses of trapped ions and initiation of the pulses in the Time-Of-Flight instrument” and “means for adjusting the delay to improve the duty cycle efficiency of ions with the second mass to charge ratio.”

### CLAIMS REJECTED UNDER 35 USC 112

Claims 99 and 115 were rejected under 35 USC 112 for lacking support for the limitations “means for providing a delay between the release of the pulses of trapped ions and initiation of pulses in the Time-Of-Flight instrument” and “means for adjusting the delay to improve the duty cycle efficiency of ions with the second mass to charge ratio.”

The Examiner stated that he did not understand how the pulse is delayed between the release of the pulses if trapped ions and initiation of pulses in the Time-Of-Flight instrument and what device is used to adjust the delay. The Examiner required additional explanations.

### STATEMENT OF FACTS

On, September 3, 2002, Applicant copied Claims from U.S. Patent No. 6,285,027 in order to provoke an interference therewith. Two of those Claims, which are the only Claims pending in the application, are as follows:

99. A method of effecting mass analysis on an ion stream, the method comprising:

- (a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass to charge ratio;
- (b) subjecting the parent ions to collision induced dissociation to generate fragment ions;
- (c) trapping the fragment ions and any remaining parent ions;
- (d) periodically releasing pulses of the trapped ions into a Time-Of-Flight instrument to detect ions with a second mass to charge ratio; and
- (e) providing a delay between the release of the pulses of trapped ions and initiation of pulses in the Time-Of-Flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass to charge ratio.

115. A method of effecting mass analysis on an ion stream, the method comprising:

- (a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio;
- (b) subjecting the parent ions to collision-induced dissociation to generate fragment ions;
- (c) trapping the fragment ions and any remaining parent ions;
- (d) periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio; and
- (e) providing a delay between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio.

Claims 99 and 115 correspond respectively to original Counts 4 and 1 of the amendment to provoke an interference filed on September 3, 2002. (see p. 21-24 thereof).

On February 26, 2003, a final Office Action denying Applicant's request for an interference was mailed.

On July 23, 2003, Applicant submitted an amendment, concurrently with an RCE, Applicant canceled Claims and reduced their request to provoke an interference to be based on two counts. Counts 1 and 2 correspond, respectively, to pending Claims 115 and 99.

On December 9, 2003, Applicant Craig Whitehouse, David Welkie and Peter Berger attended an interview with the Examiner, at which it was agreed that "all limitations of Claims 99 and 115 are supported in the specification and related specifications, but that order of Claims need be more clearly shown." (see Interview Summary, of December 9, 2003)

On August 17, 2004 Applicant received a final rejection. Subsequently, Applicant filed an Appeal Brief on July 11, 2005. Applicant argued (see Appeal Brief p. 15-21) that the Claims were adequately supported by specification and that they were additionally supported by parent application U.S. Patent No. 5,689,111.

In a non-final Office Action on November 29, 2005, the Examiner raised a problem with Applicant's chain of priority to U.S. Patent No. 5,689,111.

In response, on June 2, 2006, Applicant submitted a petition to enter an unintentionally delayed claim for priority, which was finally granted on May 4, 2007. The current application is a continuation in part of 09/808,468 (US 7,019,285), which is a continuation of abandoned application 09/448,857, which is a continuation of 08/971,521 (US 6,020,586), which is a continuation of 08/689,459 (US 5,689,111). This chain of applications is clearly set forth in the corrected filing receipt. (see Corrected Filing Receipt mailed on May 2, 2007).

On April 10, 2008, David Welkie (employee of Applicant), Peter Berger and Tuvia Rotberg conducted a second personal interview with Examiner Kiet Nguyen and his Supervisory Examiner, Robert Kim. It was agreed<sup>1</sup> that the sole issue remaining in the case was whether or not there is adequate support in the specification for the limitation of “providing a delay.” Examiner Kim requested for Applicants to supply evidence supporting their use of the term “delay.” Applicant submitted such evidence (attached hereto under the “Evidence” heading) with their preliminary amendment, which was filed concurrently with a Request for Continued Examination on April 18, 2008.

On June 17, 2008, the Examiner issued a final rejection

On October 29, Applicant filed a Notice of Appeal and a Pre-Appeal Brief Request for Review. On February 5, 2009, Applicant received a Notice of Panel Decision affirming the Examiner’s position.

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<sup>1</sup> On page 5 of the Office Action mailed June 17, 2008, the Examiner stated that he did not agree “that there is no need to show particular devices for carrying out the method...” There may have been a disagreement between Examiners Nguyen and Kim, but regardless, Applicants maintain that drawings are not necessary as discussed below.

### ARGUMENT

The method set forth in the Claims is a method of operating a mass spectrometer. In operation, an ion packet is released from an ion guide into a pulsing region of a mass spectrometer. Once in the pulsing region, it is propelled down a Time of Flight tube for mass to charge analysis. However, not all ion packets travel from the ion guide to the pulsing region at the same speed. A heavier packet will travel slower and thus require more time to arrive in the pulsing region as compared to a packet of smaller size. The invention takes account of this fact by timing the release of an ion packet from the ion guide with the TOF pulse. Said differently, the invention provides a delay between the release of pulses of trapped ions and the initiation of pulses in the Time-Of-Flight instrument. This ensures that an ion packet will be located in the “sweet spot” when the TOF pulse is initiated.

This method is claimed as “providing a delay between the release of the pulses of trapped ions and initiation of pulses in the Time-Of-Flight instrument.” This refers to the delay between the release of one ion packet from the guide and the subsequent pulsing of that ion packet from the TOF pulsing region into the TOF flight tube for mass to charge analysis.

The terms “providing a delay” and “adjusting the delay” are recited in step (e) of each of the pending Claims. Applicants’ arguments with respect to support for these limitations apply equally to Claim 99 and Claim 115 and they therefore will not be repeated for each Claim. Moreover, Applicant maintains that the terms “providing” and “adjusting” are linked, such that a finding of support for the term “providing” will also support the limitation of “adjusting.” This will become more clear with Applicant’s argument below.

Ultimately, the single significant remaining issue in this case is one of semantics: The Examiner contends<sup>2</sup> that the word ‘delay’ means essentially that an event occurs later than expected, such as, when a bus is late, it has been ‘delayed’, or when

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<sup>2</sup> The Examiner stated his position re the term “delay” in an in-person interview of April 10, 2008

some process or activity lasts longer than it should have, such as when a baseball game is 'delayed' on account of rain. Consequently, the Examiner argues that the term 'delay', as it is used in count 1, would not necessarily be understood to mean '... timing the release of ion packet...with the TOF pulse...'. In other words, the Examiner argues that the term 'delay' would not be understood to describe the 'timing' of two events – one being the release of trapped ions and the other being the TOF pulse – as described in the instant specification. Applicant disagrees with the Examiner's interpretation and respectfully submits that the timing of one event with respect to a second event imposes a time relation between the two events – which is a delay. That is, one event is delayed with respect to the other. Stated differently, there is a delay (noun) between the occurrences of two events. The Examiner seems to argue that "delay" can only be used as a verb – to delay. But the word "delay" is both a noun and a verb, and it is properly used in this application as a noun. In fact this is precisely the meaning of 'delay' as it used in the '027 patent, as well as in the '111 patent, the parent of the instant application.

It is respectfully submitted that in any technical art involving the time coordination of two or more electronically generated pulses, including the art of the instant specification, that is, time-of-flight mass spectrometry, the term 'delay' is, in fact, used precisely to describe the time relation, or 'timing', between two electronic pulses, or events. Hence, the 'timing' of one event with another event, and a 'delay' between two events, means exactly the same thing to those skilled in the art.

#### SUPPORT FOR "DELAY"

As discussed in the interview of April 10, the only remaining substantive issue in this case is whether or not the use of the term 'delay' in count 1, step (e) is adequately supported, given that this term does not appear in the specification of the instant application (that is, without considering the parent US Pat. No. 5,689,111).

Applicants assert, as in previous Office Action Responses, that sufficient support for this step is found in the current specification, and that even stronger support is found in parent U.S. Patent No. 5,689,111



To reiterate the arguments presented in previous Office Action Responses, it was stated<sup>3</sup>:

“We contend that support for step (e) is found initially in the instant specification pg. 24, lines 8-10 which state:

“Instead, *trapping and the timed release of ions* from the multipole ion guide *is a preferred method for improving duty cycle.*”

This teaching introduces the concept of improving the duty cycle by a process of trapping ions and properly timing their release to the TOF. This concept is elaborated on, following a detailed discussion of different ways of performing the trapping step, in subsequent passage on pg. 26, line 6 – pg. 27, line 5:

“By either trapping method, ions continuously enter ion guide 16 even while ion packets are being pulsed out exit end 24. The time duration of the ion release from ion guide exit 24 will create *an ion packet 52 of a given length* as diagrammed FIG. 2. As *this ion packet moves through lenses 27 and into pulsing region 30* some *m/z TOF partitioning can occur* as diagrammed in FIG. 3. The m/z components of ion packet 52 can occupy different axial locations in pulsing region 30 such as separated ion packets 54 and 56 along the primary ion beam axis. Separation has occurred due to the velocity differences of ions of different m/z values having the same energy. The degree of m/z ion packet separation is in part a function of the initial pulse duration. The longer the time duration that ions are released from exit 24 of ion guide 16, the less m/z separation that

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<sup>3</sup> see e.g. Preliminary Amendment of April 18, 2008 p. 6-9

will occur in pulsing region 30. *All or a portion of ion packet 52 may fit into the sweet spot of pulsing region 30. Ions pulsed from the sweet spot in pulsing region 30 will impinge on the surface of detector 38.* If desired, a reduced  $m/z$  range can be pulsed down flight tube 42 from pulsing region 30. This is accomplished by controlling the length of ion packet 52 and timing the release of ion packet 52 from ion guide 16 with the TOF pulse of lenses 34 and 35. *A time separated  $m/z$  ion packet consisting of subpackets 54 and 56 just before the TOF ion pulse occurs is diagramed in FIG. 3* Ion subpacket 56 of lower  $m/z$  value has moved outside the sweet spot and will not hit the detector when accelerated down flight tube 42. Ion subpackets 57, originally subpackets 54, are shown just after the TOF ion pulse occurs. These subpackets will successfully impinge on detector 38. The longer the initial ion packet 52 the less mass range reduction can be achieved in pulsing region 30. *With ion trapping in ion guide 16, high duty cycles can be achieved and some degree of  $m/z$  range control in TOF analysis can be achieved independent or complementary to mass range selection operation with ion guide 16.*" (Emphasis ours)

This passage first describes a pulse, or packet, of ions of a given length (depending on the trap pulse duration) being pulsed out of the ion guide trap. Then, "*As this ion packet moves through lenses 27 and into pulsing region 30 some  $m/z$  TOF partitioning can occur ...*". In other words, it takes some time for the pulsed ion packet to travel from the ion guide trap to the pulsing region of the TOF, and, obviously, the TOF push-pull pulse will not be activated until the ion packet, or some portion of the packet, has arrived within the TOF 'sweet spot', that is, the region within the TOF pulse region from which ions are able to reach the TOF detector once the TOF pulse occurs. This time

delay is expressed explicitly in this passage by “... *timing the release of ion packet 52 from ion guide 16 with the TOF pulse of lenses 34 and 35* A time separated *m/z* ion packet consisting of subpackets 54 and 56 just before the TOF ion pulse occurs is diagramed in FIG 3.” ‘Timing the release of ion packet...with the TOF pulse...’ is the same as ‘providing a delay between the trap release of the pulses of trapped ions and the initiation of push-pull pulses in the time of flight instrument.’ Such a delay is even more explicitly described in the ‘111 description, and will be discussed in detail below.

#### SUPPORT FOR “ADJUSTING THE DELAY...”

The second part of step (e) is ‘... and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio’. The passage from the instant application quoted above includes the statements: “All or a portion of ion packet 52 may fit into the sweet spot of pulsing region 30. Ions pulsed from the sweet spot in pulsing region 30 will impinge on the surface of detector 38.” In other words, this passage teaches that all ions of an ion packet may be detected in the TOF, provided that they are located within the sweet spot of the TOF pulsing region at the time that the TOF pulse occurs. Now, as is known to one of skill in the art, all ions of an ion packet of a particular mass-to-charge ratio will be located within the sweet spot of the TOF pulsing region only if the timing of the TOF pulse occurs after a particular time delay relative to the ion guide trap release pulse. Hence, it would seem to be clear that this passage supports the second part of step (e) ‘... adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio’.

Notwithstanding the even more explicit support found in the parent ‘111 patent, the central issue seems to be whether ‘...*timing the release of ion packet...with the TOF pulse...*’, as found in the instant specification, is substantively the same thing as the phrase in step (e), ‘providing a delay between the trap release of the pulses of trapped ions and the initiation of push-pull pulses in the time of flight instrument.’ Applicants contend that the ‘timing’ of one event with respect to a second event means that there is a time relation between the two events – one is later than the other. There is a “delay” between the start of one and the other. Because the TOF pulse must come after the

release of the ion packet from the ion trap, since the ion packet takes some time to travel from the ion trap exit to the TOF pulse region, the phrase found in the instant application, '...timing the release of ion packet...with the TOF pulse...', is the same thing as the phrase in count 1, step (e), 'providing a delay between the trap release of the pulses of trapped ions and the initiation of push-pull pulses in the time of flight instrument'

In view of the above, Applicant believes that the Examiner erred in rejecting Claims 99 and 115 under 35 USC 112 on the basis of lack of support or the limitations "providing a delay" and "adjusting the delay" in the current specification.

#### SUPPORT FOR STEP (E) IN PARENT U.S. PATENT No. 5,689,111

Applicant further maintains that there is no 35 USC 112 inadequacy regarding step (e) when the description of parent patent '111 is considered, as was reviewed in the Office Action Reply of December 18, 2007, but which the Examiner seems to have failed so far to take into account. Those arguments are repeated below:

The above arguments for support for step (e) are further bolstered by considering the U.S. Patent No. 5,689,111, which describes in explicit detail the pulsed release of ions from an ion guide trap, and the improvement in duty cycle of an ion with a particular mass-to-charge ratio by adjusting the delay between the release of the pulses of trapped ions and initiation of TOF pulses. In the '111 description, Col. 8, lines 1-28 read:

"As an example to the ion storage mode of operation, let us again use the same mixture of ions M1, M2, and M3 of ionic masses 997, 508 and 118 as used above in continuous mode of operation. As shown in FIG. 4, and FIG. 6 the pulsed ion beam of duration  $t_1$  from the region 72 is injected between the parallel plates 23 and 24 when the plates are initially held at the absence of an electric field, i.e. voltage level 79 on the repeller lens 23. According to the above equation (3), lighter ions moving faster than the

heavier ions, the three masses will start to separate from each other in the region 26. After a certain variable delay  $t_2$ , the electric field in the region 26 is pulsed on for a short period of time  $t_3$  by the repeller plate 23. The delay time  $t_2$  can be changed to allow different sections of the original ion beam, i.e. different  $m/z$  packages, to accelerate perpendicular to their original direction towards the flight tube 35 to be detected for mass analysis. In this example, a delay time  $t_2$  was chosen to pulse only a narrow range of ions centered around mass (M2) 53 which were accelerated in the direction 63 at the instant the field was turned on. At the same instant, both the masses M1 52 and M3 54 will hit the sides of the lenses moving in the approximate direction 62 and 64 and will not be detected by the mass analyzer.”

This passage describes ‘providing a delay (i.e.,  $t_2$ ) between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument,’ in the passage “After a certain variable delay  $t_2$ , the electric field in the region 26 is pulsed on”, while ‘and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio’ is described by “...delay time  $t_2$  can be changed to allow... different  $m/z$  packages... to be detected for mass analysis... a delay time  $t_2$  was chosen to pulse only a narrow range of ions centered around mass (M2) 53 ...”. The resulting improvement in the duty cycle is demonstrated in the subsequent description of demonstrated experimental results in Col. 8, lines 44-67 through Col 9, lines 1-16, which read:

“FIGS. 7A and 7B show the actual experimental results acquired using both the continuous and ion storage mode of operations for a sample using a mixture of ions used in the above examples. The actual sample was a mixture of three compounds Valine, tri-tyrosine, and hexa-tyrosine. Upon

electrospray ionization of this mixture, the predominant molecular ions with nominal masses 118, 508, and 997 are generated in the ionization source 10. The bottom trace of FIG. 7A shows all three of these ions detected and registered as peaks 73, 71, and 74 when the mass spectrometer was in the continuous mode of operation. The top trace mass spectrum in FIG. 7A shows the results when the mass spectrometer was changed to the ion storage mode of operation. Both modes were acquired in similar experimental conditions. The acquisition rate i.e. the repetition rate counted by the repeller lens was 8200 per second. Each trace represents 4100 full averaged scans. As seen from the top spectral trace, there is only one predominant registered peak 72 in the spectrum. This peak corresponds to a molecular ion 508 enhanced in signal strength by about a factor of ten with respect to the peak 71 in continuous mode of operation. For the reasons explained in above examples, both of the molecular ions 118 and 997 are absent from the ion storage mode spectral trace as expected. The signal intensity increase comes from the fact that all of the ions that would otherwise be lost in the continuous ion mode were actually being stored in the ion guide for the next scan. According to the above example, for the continuous mode of operation, the approximate duty cycle calculated for the 508 peak at 8,200 scans/s would be 9% i.e. one out of every twelve ions being detected. As the experimental results suggest in the ion storage mode of operation at 8,200 scans/s in FIG. 7A, most of the lost ions predicted in the continuous ion mode were recovered.

This passage demonstrates a molecular ion 508 enhanced.. signal strength by about a factor of ten with respect to the peak 71 in continuous mode of operation ... when the mass spectrometer was changed to the ion storage mode of operation, that is, as described in the previous passage, by providing a delay between the trap release and the TOF pulse and adjusting the delay to maximize the intensity of the m/z 508 ion, resulting from an improvement in duty cycle relative to continuous beam operation. Hence, there is sufficient support for step (e) in the current description only, and even stronger support when considering the description of parent patent '111. While the explicit description of the method step (e) is discussed in detail in the May 19, 2004 Response, as reiterated above, the means for performing this method step (e) is further described explicitly in the '111 patent, col. 7, line 59 through col. 8, line 6:

“FIG. 6 shows the driving mechanism and the timing sequence between the ion guide exit lens 15 and the time-of-flight repeller lens 23 for a single cycle, i.e. a single mass spectral scan. The trace 83 shows the ion guide exit lens voltage status switching between the two voltage levels 77 and 78 and the trace 82 shows the repeller lens voltage status switching between the two levels 79 and 80. The power supply 91 sets the desired upper and lower voltage levels to be delivered to the lenses at all times. The electrically isolated fast switching circuitry 92 controls synchronously the desired voltage levels of the lens electrode 15 and the repeller plate 23 to be switched back and forth during the designated time intervals controlled by the pulse and delay generating device 93, which is an accurate timing device, which in turn is controlled by the user interface.”

In particular, this passage teaches explicitly that “a pulse and delay generating device 93 ... controlled by the user interface” is the means used to adjust the delay.

In view of the above, Applicant believes that the Examiner erred in rejecting Claims 99 and 115 under 35 USC 112 on the basis of lack of support for the limitations “providing” a delay and “adjusting” the delay in the parent 111 patent.

### OBJECTED DRAWINGS

Applicant traverses the Examiner’s objection. The claims pending in the application are method Claims. As such there is no particular feature or device that “provides a delay between the release of the pulses of trapped ions and initiation of pulses...” Rather such delay is achieved by practicing the method of the invention as illustrated below. The same is true for “adjusting the delay to improve the duty cycle efficiency of ions...” Applicant notes that the Examiner refers to the above-mentioned steps as a “*means* for providing...” and a “*means* for adjusting.” However, Applicant claims “*the step* of adjusting” and “*the step* of providing” and not a *means* of “adjusting” and “providing.” The claimed invention is not limited to any particular device or apparatus. Applicant additionally takes note of the comments made in the 35 USC 112 rejection in which the Examiner asks “what is the device that is used to adjust the delay...” There is no particular device that is used to adjust the delay. Applicant claims the method steps of providing a “delay” as described above.

In view of the above, Applicant believes that the Examiner erred in requiring drawings in support of the above-mentioned method steps.



## APPENDIX

### CLAIMS SECTION

1-98. (Cancelled)

99. (Rejected) A method of effecting mass analysis on an ion stream, the method comprising:

- (a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass to charge ratio;
- (b) subjecting the parent ions to collision induced dissociation to generate fragment ions;
- (c) trapping the fragment ions and any remaining parent ions;
- (d) periodically releasing pulses of the trapped ions into a Time-Of-Flight instrument to detect ions with a second mass to charge ratio; and
- (e) providing a delay between the release of the pulses of trapped ions and initiation of pulses in the Time-Of-Flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass to charge ratio.

100-114. (Cancelled)

115. A method of effecting mass analysis on an ion stream, the method comprising:

- (a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio;
- (b) subjecting the parent ions to collision-induced dissociation to generate fragment ions;
- (c) trapping the fragment ions and any remaining parent ions;
- (d) periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio; and
- (e) providing a delay between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio.

116-120. (Cancelled)

## CLAIM SUPPORT AND ANALYSIS

99. A method of effecting mass analysis on an ion stream, the method comprising:

- (a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass to charge ratio; **{p. 15, lines 17-19}**
- (b) subjecting the parent ions to collision induced dissociation to generate fragment ions; **{p. 14, lines 4-7; p. 15 21-22}**
- (c) trapping the fragment ions and any remaining parent ions; **{p. 3, lines 21-23 – p. 4, line 1; p. 16, lines 4-9}**
- (d) periodically releasing pulses of the trapped ions into a Time-Of-Flight instrument to detect ions with a second mass to charge ratio; **{p. 15, lines 1-4; p. 16 lines 7-9}** and
- (e) providing a delay between the release of the pulses of trapped ions and initiation of pulses in the Time-Of-Flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass to charge ratio **{p. 13, lines 5-12; p. 22, lines 18-19; p. 24, lines 8-10; p. 26, lines 15-19}**

115. A method of effecting mass analysis on an ion stream, the method comprising:

- (a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio; **{p. 15, lines 17-19}**
- (b) subjecting the parent ions to collision-induced dissociation to generate fragment ions; **{p. 14, lines 4-7; p. 15 21-22}**
- (c) trapping the fragment ions and any remaining parent ions; **{p. 3, lines 21-23 – p. 4, line 1; p. 16, lines 4-9}**
- (d) periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio; **{p. 15, lines 1-4; p. 16 lines 7-9}** and
- (e) providing a delay between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio. **{p. 13, lines 5-12; p. 22, lines 18-19; p. 24, lines 8-10; p. 26, lines 15-19}**

## **EVIDENCE**

Support for Applicant's interpretation of the term "delay" can be found in many sources. For example, the following is found in the on-line source Wikipedia regarding devices well-known as 'delay generators':

### **"From Wikipedia, the free encyclopedia**

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A **digital delay generator** is a piece of [electronic test equipment](#) that provides precise [delays](#) for triggering, syncing, [delaying](#) and gating [events](#). The digital delay generator is similar to a [pulse generator](#) in function but with a digital delay generator [the timing resolution](#) is much finer and the [delay](#) and width [jitter](#) much less.

Some manufacturers, calling their units **digital delay and pulse generators**, have added independent amplitude polarity and level control to each of their outputs in addition to both [delay](#) and width [control](#). Now each channel provides its own [delay](#), width and amplitude control, with the triggering synchronized to an external source or internal rep rate generator - like a general-purpose [pulse generator](#).

Some delay generators provide precise [delays](#) (edges) to trigger devices. Others provides precise [delays](#) and widths to also allow a gating function. Some [delay](#) generators provide a single channel of [timing](#); others provide multiple channels of [timing](#).

Digital delay generator outputs are typically logic level, but some offer higher voltages to cope with [electromagnetic interference](#) (EMI) environments. For very harsh environments, optical outputs and/or inputs, with fiber optic connectors, are also offered as options by some manufacturers. In general, a delay generator operates in a 50 ohm transmission line environment with the line terminated in its characteristic impedance to minimize reflections and timing ambiguities.

Historically, digital delay generators were single channel devices with delay-only (see DOT reference below). Now, multi-channel units with delay and gate from each channel are the norm. Some allow referencing to other channels and combining the timing of several channels onto one for more complex, multi-triggering applications. Multiple-lasers and detectors can be triggered and gated. (see second reference on "Experimental study of laser ignition of a methane/air mixture by planar laser-induced fluorescence of OH." Another example has a channel pumping a laser with a user-selected number of flash lamp pulses. Another channel may be used in Q-switching that laser. A third channel can then be used to trigger and gate a data acquisition or imaging system a distinct time after the laser fires. (see sensorsportal.com reference below) A delay generator can also be used to delay and gate high speed photodetectors in high speed imaging applications. (see reference on high speed photography below)

Digital delay generators are usually the heart of the timing for larger systems and experiments. Users generally create a GUI, graphical user interface to provide a single control to the entire system or experiment. Digital delay generator manufacturers have added remote programming schemes that facilitate the creation of such GUI's. Industry standards such as GPIB, RS232, USB and ethernet are available from a variety of manufacturers.

Experimental fluid dynamics uses digital delay generators in its investigations of fluid flow. The field of PTV, particle image velocimetry, encompasses several subsets which would use digital delay generators as the main component of its timing where multiple lasers may be triggered. Multiple channels may trigger multiple laser. A single channel with multiplexed timing or operating in a burst mode may trigger a laser with multiple pulses.

LIDAR applications use digital delay generators. A channel is used to trigger a laser. A second channel is used to provide a delayed gate for the data acquisition system. Gating allows regions of interest to be processed and stored while ignoring the bulk of unwanted data."

In view of the above, from this description, a 'delay' is well-known to those skilled in the art to refer to the controlled time period between one electronic pulse or transition to a subsequent pulse or transition. Further, the incorporation of a delay between two or more pulses is referred to as the 'timing' of the two or more pulses. Hence, the phrase found in the instant application, '...timing the release of ion packet...with the TOF pulse...', is understood by the skilled person to mean the same as 'providing a delay between the trap release of the pulses of trapped ions and the initiation of push-pull pulses in the time of flight instrument.' of count 1 step (e), because it is well understood that 'timing two events' means 'providing a delay between the first and second event'.

This is well understood not only in the art of time-of-flight mass spectrometry instrumentation, but also in the art of many technical disciplines, such as in the art of integrated circuit developments, in which the timing between two applied voltage pulses must be controlled. Hence, there are commercial products that have been known and available for decades which provide the specific capability of generating two voltage pulses, where a second voltage pulse can be generated a definite and controlled time period after the first voltage pulse. This time period is referred to generally as the time 'delay' between the two pulses, and, equivalently, such delay generators are generally known to be used to control the 'timing' between the two pulses. Hence, the commercial products that provide this capability are referred to generally as 'delay generators' or 'digital delay generators'.

For example, one typical commercial product is the Model DG535 Digital Delay Generator manufactured and sold by Stanford Research Systems.

According to the web site for this product

(<http://www.thinksrs.com/products/DG535.htm>):

#### **"Features and Specifications**

The DG535 Digital Delay and Pulse Generator provides four precisely-timed logic transitions or two independent pulse outputs. The delay resolution on all channels is 5 ps, and the channel-to-channel jitter is less than 50 ps. Front-panel BNC outputs deliver TTL, ECL, NIM or variable level (-3 to +4 V) pulses into 50  $\Omega$  or high impedance loads. The high accuracy, low jitter, and wide delay range make the DG535 ideal for laser timing systems, automated testing, and precision pulse applications.

### Delay Outputs

There are four delay output channels: A, B, C and D. The logic transitions of these outputs can be delayed from an internal or external trigger by up to 1000 seconds in 5 ps increments. The T0 pulse, which marks the beginning of a timing cycle, is generated by the trigger signal. The insertion delay between an external trigger and the T0 pulse is about 85 ns.

Delays for each channel may be "linked" to T0 or any of the other delay channels. For instance, you can specify the delays of the four channels as:

$$A = T0 + 0.00125000$$

$$B = A + 0.00000005$$

$$C = T0 + 0.10000000$$

$$D = C + 0.00100000$$

In this case, when the A delay is changed, the B output will move with it. This is useful, for instance, when A and B specify a pulse and you want the pulse width to remain constant as the delay of the pulse is changed. Regardless of how the delay is specified, each delay output will stay asserted until 800 ns after all delays have timed out. The delays will then become unasserted, and the unit will be ready to begin a new timing cycle.

## Pulse Outputs

In addition to the four delay outputs, there are four pulse output channels: AB, -AB, CD and -CD. The leading edge of the AB pulse coincides with the leading edge of the earlier of A or B, and the trailing edge of AB coincides with the leading edge of the later of B or A. For instance, in the previous example, a 50 ns pulse would appear at the AB output and a 1 ms pulse at CD. Pulses as short as 4 ns (FWHM) can be generated in this manner. The complementary outputs (-AB and -CD) provide a pulse with identical timing and inverted amplitude.”

It is clearly understood from this description that the time difference between the time of one output transition or pulse and another output transition or pulse is called the ‘delay’ between the two output transitions or pulses, and that providing such a delay is the same as ‘timing’ one output with respect to the other output.

Similar delay generators from other manufacturers include: Model 565 Digital Delay Pulse Generator from Berkeley Nucleonics; the Model 416A Gate and Delay Generator from Ortec; the Model 2323A Gate/Delay Generator from LeCroy; the Model V850/V851 4- and 6-Channel Digital Delay Generators; and the Model 9650A precision four channel digital delay generator from Signal Recovery, which, from their web site, states: “for general timing use (especially acceleration pulse timing) in TOF-MS systems”. This is further evidence that timing one pulse with another in TOF MS systems is the same as providing a delay between the pulses

In U S Patent No. 5,689,111, col. 2, lines 39-50, the timing between the pulsed release of ions from the ion trap and the pulsed acceleration of ions in the TOF is described in terms of the timing between these two pulses:

“Also unique to this embodiment is the fact that the ion packet pulse out of the linear two dimensional multipole ion guide forms a low resolution time of flight

separation of the different m/z ions into the pulser where the timing is critical between when the pulse of ions are released from the linear two dimensional multipole ion guide and the time at which the pulser is activated. This is to say that the linear two dimensional multipole ion guide pulse time and the delay time to raise the pulser can be controlled to achieve 100% duty cycle on any ion in the mass range or likewise a 0% duty cycle on any ion in the mass range or any duty cycle in between.”

This passage demonstrates in a document prior to the instant specification that the timing between the trap release pulse and the TOF pulse is the same as the delay time between the two events.

Further, U.S. patent No. 4,988,879 claims a method as follows:

“26. In a method for generating a burst of gaseous ions of a solid organic material comprising the steps of

- a. providing the solid organic material as a deposit on a non-porous, inorganic oxide, solid support surface,
- b. striking the deposit with a pulse of a first laser to desorb the deposit off of the surface and give rise to a cloud of gaseous molecules of the organic material, and
- c. thereafter passing through the cloud of gaseous molecules a beam of a second laser to effect ionization of a portion of the gaseous molecules which it strikes, thereby producing the burst of gaseous ions;

the improvement comprising employing as the beam of the second laser a pulse of the second laser and timing the pulse to contact the largest fraction of the gaseous molecules.”

Support for this claim is found in col. 9, line 62 through col. 10, line 21, which states:

“In a preferred embodiment of the overall ionization process of this invention, the sample ... is deposited as a solid film (i.e., a layer) on an inorganic oxide surface



... A laser beam having the properties of wavelength and fluence suitable for desorbing and vaporizing but not ionizing the solid sample is directed upon the film for a controlled time period adequate to effect desorption and vaporization. Neutral molecules are generated in a fast desorption process. ... The cloud of desorbed molecules then expands into the high vacuum chamber between two electrodes which form the acceleration region of a linear time of flight ("TOF") mass spectrometer. In a second step these molecules are ionized by a beam (preferably a pulse) of an ultraviolet laser having the properties of wavelength, fluence and pulse duration to bring about resonance-enhanced multiphoton ionization ("REMPI") of the vaporized molecules. An appropriate delay between the desorbing laser pulse and the ionizing laser pulse is chosen so that the ionizing laser pulse intercepts as many molecules as possible.

The time delay between the two laser pulses should be such as to permit the ionizing laser beam to contact as many particles as possible. Generally, this is achieved when the period from the beginning of desorption to the beginning of ionization is adjusted on the order of from about 20 to about 180 usec and preferably from about 30 to about 150 usec."

Hence, the 'timing' between the two laser pulses referred to in the claim is described in the specification as a delay between the two laser pulses, demonstrating equivalence between 'timing two pulses' and 'providing a delay between two pulses'. Therefore, similarly, there should be no ambiguity when equating the phrase in count 1 step (e) of the instant application, 'providing a delay between the trap release of the pulses of trapped ions and the initiation of push-pull pulses in the time of flight instrument.', and the description in the text of the instant application, '...timing the release of ion packet...with the TOF pulse...'. .

Applicant believes that as a result of the above, all will agree that the pending Claims are supported by the Specification and interfere with US patent No. 6,285,027. It is thus respectfully requested that an interference be accordingly declared.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'T. Rotberg', with a long horizontal flourish extending to the right.

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